## REMARKS

The November 20, 2003 Official Action and the references cited therein have been carefully reviewed. In view of the amendments presented herewith and the following remarks, favorable consideration and allowance of this application are respectfully requested.

The Examiner has stated that claims 20-37 and claims 40-43, drawn to non-elected inventions are withdrawn from consideration.

At the outset, we note a contradiction in the Office Action with respect to Claims 31-37. On the summary sheet, Claim 31-37 are referred as both drawn to a non-elected invention and therefore withdrawn from consideration, as well as included in the claims that were examined on their merits in the present Office Action. Inasmuch as the Examiner has addressed the merits of claims 31-37 in the Official Action, Applicants presume these claims are currently being examined for patentability. Clarification of this error is respectfully requested.

On page 2 of the Office Action, the Examiner has objected to claims 31-35, and dependent claims 31-34 and 36-37 for being dependent on non-elected claims. The dependencies of the foregoing claims have been rectified such that they now depend on claims currently under examination. Specifically, Claim 31 has been amended as an independent claim and thus does not refer to any other claims, including claim 20. Claim 35 has been amended to depend from claim 31. Claim 32 depends from claim 31. Claims 33 and 34 depend from claim 32. Claim 35 depends from claim 34. Claim 36 depends from claim 31. Claim 37 depends from claim 36. Thus, the Examiner's objections to the claims as being dependent on non-elected claims have been rendered moot.

The Examiner has rejected claims 1-19 and 31-37 under 35 U.S.C. §112, second paragraph as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention.

Claims 1-3, 6-8, 11, 19 and 31-37 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement.

On pages 6 and 7 of the Office Action, the Examiner has rejected claims 1-10, 13-15, and 31-37 under 35 U.S.C. §112, first paragraph, asserting that the claims are not fully enabled by the disclosure in the application.

The Examiner has rejected claims 11-12 under 35 U.S.C. §102(b) as being allegedly anticipated by Kim *et al.*

Finally, claims 1, 3, 4, 6 and 7 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Smith *et al*, as evidenced by Kubota *et al.*, and in view of Hynes *et al.*

The objections and rejections summarized above constitute the entirety of objections and rejections raised by the Examiner in the November 20, 2003 Office Action. No other issues are pending in the present application. Applicants respectfully submit that the claims as presently amended are in condition for allowance. Each of the above-noted rejections under 35 U.S.C. §§112, first and second paragraphs; 35 U.S.C. §102(b); and 35 U.S.C. §103(a) is, therefore, respectfully traversed.

**THE METES AND BOUNDS OF CLAIMS 1-19 AND 31-37 AS AMENDED ARE CLEAR TO ONE OF ORDINARY SKILL IN THE ART AND SATISFY REQUIREMENTS OF 35 U.S.C. §112, SECOND PARAGRAPH**

The Examiner has rejected claims 1-19 and 31-37 as being allegedly indefinite for failing to point out and distinctly claim the subject matter which the applicant regards as the invention.

In particular, the Examiner states that

- the nature of binding between the CCT complex and substrate in claim 1 is unclear,
- the recitation of "substrate" in claims 7 and 8 is vague and indefinite,
- claim 11 is unclear with regard to the recitation of "determining,"
- it is allegedly unclear how claim 13 further limits claim 12 and how claims 14 and 15 further limit claim 13,
- claim 31 fails to relate the extent of binding of candidate mimetics with the objective of screening for mimetics,
- the metes and bounds of what constitutes a peptide fragment in claims 3,12 and 13 is unclear,
- claims 9 and 16 are vague and indefinite for the recitation of Figure 9,
- claim 31 is unclear as to what constitutes the "active portion thereof"
- claim 32 is vague and indefinite in the recitation of "screening...for biological activity as the metes and bounds of "biological activity" are not defined, and

- claim 36 is unclear with regard to what constitutes the "CCT substrate binding site complex or active portion thereof" and with regard to the dependence of the metes and bounds upon the product of claim 27. ,

The relevant inquiry in determining whether a given claim satisfies the requirements of 35 U.S.C. §112, second paragraph, is whether the claim sets out and circumscribes a particular area with a reasonable degree of precision and particularity such that the metes and bounds of the claimed invention are reasonably clear. In re Moore, 169 U.S.P.Q. 236 (CCPA 1971). Applicants respectfully submit that with respect to claims 1-19 and 31-37 of the present application, such inquiry must be answered in the affirmative.

The definiteness of claim language may not be analyzed in the abstract, but must be considered in light of the teachings of the prior art and of the particular application disclosure, as it would be interpreted by one having ordinary skill in the art. In re Moore, supra. The claims have been amended as set forth below to remove any perceived lack of clarity.

1.1 Claim 1 has been amended to recite that the binding member inhibits the binding of the CCT substrate to the CCT complex.

1.2 Claims 7 and 8 have been amended to specify that the substrate is the substrate from which the binding member is derived.

1.3 The Examiner has objected that it is unclear if "determining" is directed to a qualitative or quantitative measure. However, it is submitted that the term covers either qualitative or quantitative measurement, and this does not lead to the claim being vague or indefinite. The person skilled in the art would clearly understand that any method of determining binding between the candidate binding member and the CCT apical domain would fall within the claims, and would have no difficult in identifying the metes and bounds of the claim.

1.4 The Examiner has objected that it is unclear how claim 13 further limits claim 12, and how claims 14 and 15 further limit claim 13.

Claim 13 as filed on entry to the US national phase contained an error. It should have referred to a peptide or peptide fragment having an amino acid sequence corresponding to the amino acid sequence of a CCT substrate (and not the CCT apical domain), in accordance with claim 13 of the originating PCT application. This correction has been made to the present amended claims, thus imparting clarity to the claim.

1.5 The Examiner has asserted that claim 31 fails to relate the extent of binding of the candidate mimetic to the CCT substrate binding site with the objective of screening for mimetics. The claim has now been amended to recite that a mimetic of the binding member binds to the CCT substrate binding site or reduces the extent of binding of the binding member to the CCT substrate binding site.

1.6 The Examiner asserts that claims 3, 12 and 13 recite peptide fragments, and alleges that the metes and bounds of the claim are unclear because a peptide fragment could be a single amino acid or even a part thereof. For clarity, reference to "peptide fragment" has been deleted from the claims.

1.7 The Examiner has alleged that claims 9 and 16 and indefinite in their dependence of Figure 9. (It is respectfully noted that claims 9 and 16 in fact referred to Figure 10). This has been addressed by amending the clams to refer to the appropriate SEQ ID NOs 1-15.

1.8 The Examiner has objected that claim 31 is unclear as to what constitutes an active portion of a CCT binding site. Reference to the active portion of the CCT binding site has been deleted from the claim. This does not affect the claim scope.

1.9 Claim 32 is objected to as vague and indefinite in the recitation of "screening ... for biological activity" without a definition of the metes and bounds of "biological activity". Claim 31 has been amended to state the method further comprises screening the candidate mimetic for the ability to affect the normal biological activity of CCT in the cell. Inasmuch as the normal biological activity of CTT is set forth throughout the specification, Applicants submit that the metes and bounds of the phrase would be readily appreciated by the skilled person.

1.10 Claim 36 is objected to as it is allegedly unclear what constitutes the "CCT substrate binding complex or active portion thereof". This term has been replaced by referring to the CCT complex or a part thereof having a substrate binding site.

1.11 Finally, the Examiner has objected that claim 35 is unclear in as much as it refers back to product claim 27. Claim 35 has been amended so as to be dependent on method claim 31.

The amendments and comments provided above address all the of the Examiner's objections to the claims and serve to clarify the metes and bounds of the claimed subject matter. Accordingly, withdrawal of each of the claim rejections under 35 U.S.C. §112, second paragraph is respectfully requested.

## THE CLAIMS AS AMENDED FULLY SATISFY THE WRITTEN DESCRIPTION REQUIREMENT OF 35 U.S.C. §112, FIRST PARAGRAPH

The Examiner has rejected claims 1-3, 6, 7, 8, 11, 19, and 31-37 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement asserting that the claims allegedly contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention. The rejection of these claims as amended under 35 U.S.C. §112 first paragraph as allegedly lacking written description cannot be maintained. As noted in the MPEP at § 2163,

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention.

Possession may be shown in many ways. For example, possession may be shown by describing an actual reduction to practice of the claimed invention.

Furthermore, the written description guidelines set forth in the Federal Register Vol. 66, No. 4, January 5, 2001 states that "An adequate written description of the invention may be shown by any description of sufficient, relevant, identifying characteristics, so long as a

person skilled in the art would recognize that the inventor had possession of the claimed invention."(page 1105, column 3). "An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that the applicant was in possession of the claimed invention, ie: complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of characteristics." (Page 1106, column 1).

The Examiner has alleged that independent claims 1, 11 and 32 are dependent on a genus of binding members which are capable of occupying a substrate binding site on the CCT complex. The Examiner has further alleged that the binding members on which the claims are based are not adequately described, and so the method claims dependent on said binding members are also not adequately described.

However, the Examiner is incorrect in treating the claims as relating to a genus of binding members. The claims are directed to a method of **identifying** such binding members, i.e., to a system which is capable of identifying whether or not any given candidate substance assessed in the instantly claimed methods functions as a binding member. Hence, an objection based on lack of written description against the candidate binding member is inappropriate, since the nature of the candidate binding member is not a feature of the method.

Moreover, the Examiner's attention is drawn to the Trilateral Report, in response to the Questionnaire for Comparative Study on "Reach-Through Claims". In this report, assay claims for identifying agonist compounds are found to be patentable in principle, even if no worked examples have been carried out (example 2, claim 2). Provided the steps of the method are adequately described, there is not considered to be any requirement for the test substances to also be described. In light of the foregoing, withdrawal of the rejection is therefore requested.

The Examiner has rejected claims 1-10 because the skilled person would be subject to undue experimentation in order to practice the invention to the full scope of the claims which include the recitations "part thereof" in reference to "binding site". The examiner has noted that there are at least some substrates of the CCT complex which do not bind at the apical domain.

In order to practice the method of claim 1, it is not necessary that the user should have characterized precisely where on the CCT complex the substrate binds. All that is required is that the skilled person should be able to determine that the substrate does bind to the part of the CCT complex in question. The user can then proceed to use the method in respect of that part. Techniques for determining whether two proteins or protein complexes are capable of binding to each other are well known in the art.

Finally, Applicants note that third parties could readily omit part of the CCT complex, having ascertained by routine means that this omission has no detrimental effect on substrate binding (i.e., that the substrate still binds). Thus, such an amendment is unduly limiting and moreover, would conceivably allow the third party to avoid the claim while still obtaining the full benefit of the inventor's work. Applicants respectfully submit that given the detailed disclosure provided in the specification no undue experimentation is required to practice the full scope of the amended claims. Accordingly, the rejection is improper and should be withdrawn.

Claims 31-37 stand rejected because, while the Examiner acknowledges that the specification is enabling for mimetics to the binding members disclosed as the BEP peptides, the Examiner alleges that it does not reasonably provide enablement for binding members which have not been disclosed. The Examiner has based this rejection on the assertion that it would be necessary to be able to make the binding members in order to carry out the method of claims 31-37, and that the skilled person is not taught how to do this because a teaching of how to identify is not equivalent to a teaching of how to make.

Claim 31 has been amended in the present response so that it is in an independent form. It is directed to a method of finding mimetics of a binding member which comprises an amino acid sequence of 5 to 40 amino acids derived from a CCT substrate, wherein said binding member has been identified by the method of claim 1 or claim 11.

The examiner has derived the present objection from the prohibition on "reach-through" claims to products.

However, the Examiner's objection is not applicable to the present method claim, which is directed to a method of finding the mimetic. The method requires that steps be carried out resulting in the identification of a binding member, and also requires the further step of finding a mimetic of that binding member.

It is well within the capabilities of a person skilled in the art to add a further method step to the methods of claims 1 or 11, in which the binding member is used in a competitive assay for a mimetic. These further method steps are taught to the skilled person in a sufficient manner. Therefore withdrawal of the rejection is requested.

The Examiner has also rejected claims 13-15 alleging that undue experimentation would be required to practice these claims. The objection to claims 13-15 under 35 U.S.C. §112, first paragraph are rendered moot by the present amendments to the claims. Accordingly, Applicants request that the rejection be withdrawn.

**THE CLAIMS AS AMENDED ARE NOVEL OVER KIM ET AL.**

A rejection under §102(b) is warranted only when the cited reference identically discloses the subject matter of the invention as claimed. In re Bond, 15 U.S.P.Q.2d 1566 (Fed. Cir. 1990). Applicants respectfully submit that the rejection under §102(a) is not warranted in this case because Kim et al. do not disclose an identical invention.

The Examiner has rejected claims 11 and 12 under 35 U.S.C. §102(b) as being anticipated Kim *et al.* (*Trends in Biochemical Sciences*, 1994, volume **19**, pp. 543-548). Kim *et al.* observe that actin bound to CCT is localised, at least in part, inside the central channel.

It is respectfully submitted that this cited disclosure is not a method identifying a binding member, as required by claim 11. Actin is a known binding member, and the disclosure in Kim *et al.* is merely to confirm that the binding sites for actin are located on the inside faces of CCT, in the central channel. Moreover, claim 11 has now been amended to require that the binding member is capable of inhibiting binding of the CCT apical domain to its substrate. Hence, claim 11 is directed to an assay for identifying an inhibitor of substrate binding. Inasmuch as Kim *et al.* does not describe an identical method the rejection is improper and should be withdrawn.

**THE CLAIMS AS AMENDED ARE NOT OBVIOUS OVER SMITH ET AL.**

The Examiner has rejected claims 1, 3, 4, 6, and 7 under 35 U.S.C. §103(a) as being unpatentable over Smith *et al.* (Abstract from 9$^{th}$ International Congress on Immunology,

1995, page 671, abstract #3982), as evidenced by Kubota *et al.* (*Gene*, 1995, volume **154**, pp. 231-236), and in view of Hynes *et al.* (*Electrophoresis*, 1996, volume **17**, pp. 1720-1727).

Smith *et al.* report that TNF and IFN-γ induce the expression of two melanoma proteins, having homology to the N-terminal sequence of α-tubulin. It is also noted that there is a decrease in the relative abundance of the full-length tubulin molecule. Another melanoma protein which is suppressed by the combined treatment shows identity to TCP-1, a subunit of a chaperone protein.

The Examiner has taken these facts, and has applied his hindsight knowledge of the present invention to reach a number of unjustified conclusions. The Examiner is reminded of the requirement for forming a *prima facie* obviousness attack, that:

"To reach a proper determination under 35 U.S.C. §103, the examiner must step backward in time and into the shoes worn by the hypothetical "person of ordinary skill in the art" when the invention was unknown and just before it was made." **[MPEP 2142].**

"...impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art." **[MPEP 2142]**

From the information gleaned from the prior art, there would have been no reason for the skilled person to believe that the new melanoma proteins specifically interfere with CCT's action on tubulin. Nor would they have had reason to believe that these proteins bind to the TCP-1 protein. Still less would the skilled person have concluded that the reduction of TCP-1 was in some way a negative feed-back loop caused by the reduction in tubulin. All of these points are assumptions made by the Examiner, and not obtained directly from the prior art.

Moreover, the Examiner has made an error in saying that "Kubota *et al.* teach that TCP-1 is synonymous with the theta subunit of CCT (abstract)". TCP-1 is in fact the CCT-alpha subunit. The CCT complex comprises eight different subunits, and the work of the present inventors has shown that the subunits have different specificities for different substrates and sequences thereof. Therefore, even if the skilled person knew that the CCT complex as a whole was involved in the correct folding of tubulin, (s)he would not know that tubulin could bind the CCT-alpha subunit.

The present inventors have for the first time, through their determination of the CCT complex assembly, established that CCT recognizes specific sequences on the surface of proteins, and not their hydrophobic protein core. The distinct CCT subunits recognize

specific sequences of the substrate. For example, the inventors have determined that the two surface exposed loops (not hydrophobic) of actin comprise a major CCT binding site. As a result, they have recognized that specific structural domains of substrate proteins and analogues thereof can be tested according to the present claims with a reasonable expectation of success.

Without this knowledge, which the Examiner has acquired from the present application, the only conclusion that the Examiner would have drawn from the facts would have been the conclusion that was drawn by the authors themselves, namely:

"These data suggest that folding and assembly of tubulin is altered in melanoma cells treated with TNF alone, and synergistically with TNF and IFN-γ " (Smith *et al.*, lines 16-18)

The Examiner has further alleged that it would have been *prima facie* obvious to one of ordinary skill in the art to determine if the proteins produced by the melanoma cells in response to TNF or IFN-γ inhibit binding of tubulin to the CCT complex. The Examiner submits that it would have been obvious to want to seek binding members which compete with tubulin to cause decreased tubulin and actin synthesis to negatively control the increased demands for actin and protein synthesis as taught by Hynes *et al.*

However, it is respectively submitted that this formulation fails to meet the requirements for prima facie obviousness.

"To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure such as any evidence in the specification or any other evidence submitted by the applicant." **[MPEP 2142]**.

There is no suggestion in either of the documents cited by the Examiner to seek to test the peptides disclosed in Smith *et al.* in an assay method according to the present claims. Even if the general desirability of downregulating CCT activity could be derived e.g., from Hynes *et al.* (which is not conceded), then this would still not lead the skilled person to combine this teaching with Smith *et al.* Smith *et al.* contains no teaching whatsoever that the

two melanoma proteins might be responsible for the reduction in CCT action. It merely discloses that the folding and assembly of tubulin might in some way be altered in cells treated with an antiproliferative agent.

Secondly, it will be seen from the discussion under section 4.2 (above) that there is nothing in either of the prior art documents which would lead the skilled person to have a reasonable expectation of success in testing the peptides for their ability to inhibit CCT action on tubulin.

Finally, even the combination of Smith *et al.* with Hynes *et al.* does not teach all of the features of the claimed assay. The assay method of present claims 1 is specifically an assay for a binding member capable of occupying a substrate binding site on the CCT complex, where the binding member inhibits the binding of the CCT substrate and the CCT complex. There is no teaching or suggestion whatever in Smith *et al* that the melanoma proteins might be capable of binding the CCT complex or inhibiting the binding of tubulin to the CCT complex. This assumption has been made by the Examiner with hindsight. The skilled person at the time would have had no reason to design as assay having all of the features of claim 1.

Therefore, clams 1, 3, 4, 6 and 7 as amended are inventive over the documents cited by the Examiner and withdrawal of the objection under 35 U.S.C 103(a) is requested.

It is respectfully urged that this case be placed in condition for allowance. In the event the Examiner is not persuaded as to the allowability of any claim, and it appears that an outstanding issue may be resolved through a telephone interview, the Examiner is requested to telephone the undersigned attorney at the phone number given below. In the event that a fee is required, the Examiner is authorized to charge the deposit account of the undersigned 04-1406.

Respectfully submitted,
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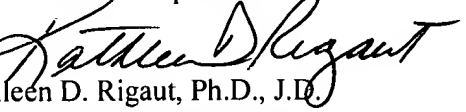
By 
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